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S3 Mitochondrial Ion Pumps

3L1

Effect of mtDNA point mutations on cellular bioenergetics

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This overview discusses the results of research on the effects of most frequent mtDNA point mutations on cellular bioenergetics. Thirteen proteins coded by mtDNA are crucial for oxidative phosphorylation, 11 of them constitute key components of the respiratory chain complexes I, III and IV and 2 of mitochondrial ATP synthase. Moreover, pathogenic point mutations in mitochondrial tRNAs and rRNAs generate abnormal synthesis of the mtDNA coded proteins. Thus, pathogenic point mutations in mtDNA usually disturb the level of key parameter of the oxidative phosphorylation, i.e. the electric potential on the inner mitochondrial membrane ($\Delta\psi$), and in a consequence calcium signalling and mitochondrial dynamics in the cell. Mitochondrial generation of reactive oxygen species is also modified in the mutated cells. The results obtained with cultured cells and describing biochemical consequences of mtDNA point mutations are full of contradictions. On the cellular level, consequences of mtDNA mutations depend on cell type (cells predominantly oxidative vs. glycolytic; cells with intensive metabolism vs. slow metabolism), genetic background, level of the penetration of a given mutation (heteroplasmy) and physiological state of cell (resting vs. activated). Still they help to elucidate the biochemical basis of pathologies and provide a valuable tool for finding remedies in the future.

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3L2

Complex effects of 17β-estradiol on mitochondrial function

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For a better understanding of earlier reported cell-protection by estrogens [1], we examined possible effects of 17β-estradiol (βE) on the mitochondrial physiology. We focussed our attention on the response of the Ca^{2+}-triggered permeability transition to βE. Due to its strongly hydrophobic properties interactions with several of the hydrophobic proteins of the mitochondrial inner membrane like the permeability transition pore (PTP) or complexes of the electron transport chain (ETC) had to be considered. Additionally, we studied βE-effects on the potassium BK-channel which very likely is functionally coupled to the PTP. Thus, we wanted to find out if the PTP and/or the BK-channel could be modulated by βE in a way that would contribute to an explanation of the cell protective effect of βE.

Mitoplasts from rat liver mitochondria (RLM) were prepared to study the PTP, and from cultured rat astrocytes to study the potassium BK-channel by single-channel patch-clamp techniques. Additionally, we investigated the respiration of intact RLM to elucidate the βE-effect on complexes of the ETC.

After application of βE our single-channel results revealed a transient increase of the open probability (Po) of both, the BK-channel and the PTP within <3 min followed by their powerful inhibition. At a high Ca^{2+}-concentration (200 μM) the Po of the PTP first increased from 0.33 ± 0.03 ($n = 3$ independent experiments; mean ± SEM) to 0.44 ± 0.04 and then decreased to zero within <5 min where it stayed. The respiration measurements demonstrate the inhibition of the Ca^{2+}-induced permeability transition, as well, though only at higher βE-concentrations (≥30 μM). An increase of endogenous- and state 2-respiration was observed already at lower βE-concentrations. Furthermore, we show that βE diminishes the phosphorylating respiration supported by the complex I-substrates (glutamate/malate) or by the complex II-substrate succinate. Taken together the results suggest that βE affects mitochondria by several modes, including partial inhibition of the activities of ion channels of the inner membrane and of phosphorylating respiration.

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Reference

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